February 2008 *Volume 4 Issue 2*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full paper

OCAIJ, 4(2), 2008 [150-155]

Synthesis and antimicrobial properties of 2-[4 -fluoro phenyl amino] - 4 -(2-naphathalene ureido)-6-(aryl ureido)-[1, 3, 5]-triazines

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Received: 26th March, 2007 ; Accepted: 31st March, 2007

ABSTRACT

Aryl ureido 1,3,5-triazines(III_{a-j}) were synthesized and tested for their antibacterial, antifungal, Photosynthesis-inhibiting, and antialgal activity. Compounds III_c was moderatively active against *E.Coli* and III_i against *B.Subtilis*. No antifungal activity was observed, and III_h possessed photosynthesis-inhibiting activity. The anti-algal activity of the compounds tested was relatively low. HPLC method for analysis of final targeted molecules are presented here.

KEYWORDS

Amaryllidaceae alkaloids;
(-)-g-Lycorane;
Asymmetric induction;
5-endo-trig cyclization.

INTRODUCTION

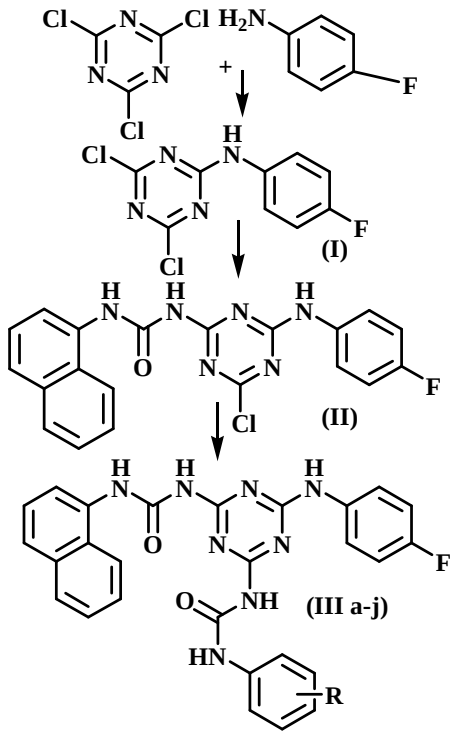
Fluoro compounds[1,2] and s-triazine[3] derivatives exhibit biological activities, as herbicide[4], antioxidant for lubricating materials[5], deodorant for treating organic sludges[6], treatment of hyper proliferative disorders[7], in plant growth regulation[8]. Urea's and thioureas have been used in the manufacturing of resins[9], glue solvents, photographic fixing agent, vulcanization accelerator and in some medicines. Its derivatives show a wide range of pharmacological properties such as diuretics[10], antibacterial[11], hypoglycemics[12], in treatment of ulcers. In view of our interest to search for new synthetic organic compounds[13] for expected use as pharmaceutical products, several derivatives of aryl ureas with s-triazine have been prepared and studied their biological activities.

RESULTS AND DISCUSSION

Cyanuric chloride and 4-Fluoro phenyl aniline was condensed in equimolar proportions. The resultant product was reacted with naphthalene urea followed by condensation with various aryl ureas to yield the corresponding 1,3,5-triazine derivatives (III_{a-j})(SCHEME 1).

Substituted ureas have been used to provide the corresponding Aryl ureido 1, 3, 5-triazines in high yields, which are also of much interest with regard to biological activity The results are listed in TABLE 1. Another important feature of this procedure is the stability of a variety of functional groups such as methyl, nitro and halides, under these reaction conditions.

The constitution of all the products has been confirmed by elemental analysis and supported by ^{1}H NMR and Mass spectra. The new aryl ureido 1,3,5-triazine



SCHEME 1

TABLE 1: Synthesis of aryl ureido 1,3,5 triazine derivatives

Entry	R	Molecular formula	Molecular weight	M.P (°C)	Yield (%)
III_a	H	$C_{27}H_{21}FN_8O_2$	436.64	202-204	70
III_b	o-CH_3	$C_{28}H_{23}FN_8O_2$	450.67	212-214	64
III_c	m-CH_3	$C_{28}H_{23}FN_8O_2$	450.67	210-212	62
III_d	p-CH_3	$C_{28}H_{23}FN_8O_2$	450.67	218-220	64
III_e	o-NO_2	$C_{27}H_{20}FN_9O_4$	481.64	232-234	64
III_f	m-NO_2	$C_{27}H_{20}FN_9O_4$	481.64	234-236	72
III_g	p-NO_2	$C_{27}H_{20}FN_9O_4$	481.64	228-230	60
III_h	o-Cl	$C_{27}H_{20}ClFN_8O_2$	470.09	206-208	70
III_i	m-Cl	$C_{27}H_{20}ClFN_8O_2$	470.09	212-214	74
III_j	p-Cl	$C_{27}H_{20}ClFN_8O_2$	470.09	220-222	72

derivatives are tabulated in TABLE 1.

Biological activity

Antibacterial, Antifungal and Photosynthesis inhibiting activity were studied for all Aryl ureido 1,3,5-triazine compounds.

Antibacterial activity

All the synthesized compounds were screened for their antibacterial against *Bacillus subtilis* and *Escherichia coli* by cup-plate agar diffusion method[14] using DMF as solvent. The solution of compounds at 50µg/ml concentration, compared with standard drugs like Amoxycillin and Griseofulvin respectively with incubation period of 36h, the results are presented in TABLE 2.

TABLE 2

Entry	R	Zone of inhibition in (ZOI) mm at 50µg/ml concentration	
		E.coli	*B.subtilis*
III_a	H	-	-
III_b	o-CH_3	4	3
III_c	m-CH_3	11	5
III_d	p-CH_3	6	5
III_e	o-NO_2	8	3
III_f	m-NO_2	3	9
III_g	p-NO_2	6	9
III_h	o-Cl	4	10
III_i	m-Cl	6	12
III_j	p-Cl	3	8

TABLE 3

Entry	R	IC_{50}(umoldm^{-})
III_a	H	-
III_b	o-CH_3	53
III_c	m-CH_3	212
III_d	p-CH_3	50
III_e	o-NO_2	21
III_f	m-NO_2	16
III_g	p-NO_2	23
III_h	o-Cl	1.2
III_i	m-Cl	1.0
III_j	p-Cl	2.3

Compounds III_c and III_i were moderately active against *Escherichia Coli* and *Bacillus subtilis* in comparison to standard drugs like Amoxycillin (20mm ZOI) and Griseofulvin (19mm ZOI), and other compounds are less active, while III_a shows no activity.

Antifungal activity

Antifungal activity was tested *in vitro* against *Candida albicans, Candida tropicalis,Candida krusel, Trichosporon beigelii, Trichophyton mentagrophytes, Aspergillus fumigatus, Absidia corymbifera* using broth microdilution method. All the compounds III_{a-j} were inactive, with an exception of derivative III_c which showed a moderate activity against *Absidia corymbifera* (MIC 60.4 umol dm^{-3}) and *Aspergillus fumigatus* (MIC 60.7µmol dm^{-3}) after 24h of incubation.

Photosynthesis-inhibiting activity in spinach chloroplast

Most of the tested compounds inhibited the photosynthetic electron transport in spinach chloroplasts. The photosynthesis-inhibiting activity of the compounds was

investigated as inhibition of oxygen evolution rate (OER) in spinach chloroplasts. IC_{50} values are given in TABLE 3. Compound III_c was most effective inhibitor of EOR. It was 50-fold more potent than other -NO_2 and -Cl compounds. Where as *ortho* and *para* derivatives III_b and III_d were approximately twice less potent than compound III_c while III_e, III_g are more than 100-fold less potent. The relatively low photosynthesis-inhibiting activity of compounds III_{h-j} is probably a consequence of their low aqueous solubility, and hence their restricted passage through the hydrophilic regions of thylakoid membranes. A comparison of compounds III_{h-j} with their analogues III_c and III_d indicates 60-100 fold decrease in activity. Photosynthesis-inhibiting activity of compound III_a could not be determined due to its incomplete solubility. The results are presented in TABLE 3.

EXPERIMENTAL

General

All the solvents and starting reagents were of AnalaR grade and are used without further purification. Glassware is oven or flame dried prior to use. Reactions are performed under argon inert atmosphere. Crude products are purified by flash chromatography using 230-400 mesh silica gel supplied by Acme chemicals limited, mumbai, India. Target compounds are analyzed for purity by analytical HPLC, which was performed using Shimadzu AT series with HP controller and Varian UV detectorusing a C-8 hypersil silica column (250mm×4.6mm). ^1H and ^{13}C NMR was recorded on Varian Gemini 200MHz and 75MHz spectrometer in DMSO-d_6 solvent. Chemical shifts were reported as parts per million downfield from an internal tetra methyl silane (TMS) standard (0.00 for ^1H NMR). ES Mass was performed at analytical division, Sai Life Sciences Limited, Hyderabad, India. Elemental analysis was performed at Indian Institute of Chemical Technology, Hyderabad, India. Anti microbial analysis were performed at Central Drug Research Institute, Lucknow, India and National Chemical Laboratory, Pune, India.

Chemistry

Aryl urea's are prepared according to known method available in literature[15]. Purities for all the target compounds are analyzed by HPLC[16] and purities >97% was obtained.

Synthesis of 4, 6-dichloro- [1,3,5] triazin-2-yl- (4-fluoro phenyl) amine (I)

To a stirred solution of 4-Fluoro aniline (5g, 0.01mol) in acetone at 0^0C was added cyanuric chloride (9.9g, 0.012mol) in acetone for 45 minutes and neutral pH was maintained with $NaHCO_3$ solution. The contents were stirred for 12 hours at 0^0C. The reaction mixture was poured on crushed ice, filtered, dried and recrystallized from absolute ethanol to give **(I)**, yield 63%. ^{1}HNMR (200MHz, DMSO-d_6): δ7.14-7.27 (Ar-H, m, 2H), δ8.02(-NH, broad, 1H), δ8.17-8.27(Ar-H, m, 2H). ^{13}CNMR (75 MHz, DMSO-d_6): 15.96, 115.96, 116.1, 116.1, 150.39, 152.53, 169.26, 169.62, 162.62. m/z 260.06 (M+1).

Synthesis of 1-[4-Chloro-6 (4-fluoro phenyl amino)-[1,3,5] triazin-2-yl]-3-naphthalen-1-yl-urea (II)

Naphthalene-1-yl- urea (5g, 0.01 mol) in acetone was added to a stirred solution of I (6.4g, 0.01 mol) in acetone at below 30^0C for 45 minutes and neutral pH was maintained with $NaHCO_3$ solution. The temperature was raised to 45^0C and stirring was continued for 12 hours. The reaction mixture was poured on crushed ice, filtered, dried, and recrystallized from absolute ethanol to give (II), yield 65%. ^{1}HNMR (200MHz, DMSO-d_6): δ7.09-7.20 (Ar-H, m, 4H), δ7.47-7.68 (Ar-H, m, 4H), δ7.96 (Ar-H, d, 1H), δ8.09-8.13 (Ar-H, m, 2H), δ10.21(-NH, s, 3H). ^{13}CNMR (750 MHz, DMSO-d_6): 114.05, 115.96, 115.96, 116.68, 120.35, 122.59, 122.66, 125.46, 125.50, 126.77, 128.26, 138.25, 147.97, 148.18, 150.38, 152.53, 170.78, 172.22, 176.43. m/z 409.67 (M+1).

Synthesis of 1-[4-(4-Fluoro phenyl amino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl]-3-aryl urea (III_{a-j})

Compound (II) (0.01mol) and Aryl urea (0.01mol) in acetone was refluxed for 6 hours. The solution was treated with crushed ice, filtered, dried and purified by flash chromarography in 30:60 ethyl acetate; hexanes (III_{a-j}) as off-white to brownish solids, yield 60-74%.

Spectral data for aryl ureido 1,3,5 triazines (III_{a-j})

1-[4-(4-Fluoro-phenyl amino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl]-3-phenyl urea (III_a)

^{1}HNMR(200MHz, DMSO-d_6): δ 7.05-7.26 (Ar-H, m, 8H), δ 7.47(Ar-H, d, 1H), δ 7.56 (Ar-H, t, 1H), δ 7.60 (Ar-H, d, 1H), δ 7.68 (Ar-H, t, 1H), δ 7.94-8.01 (Ar-H, m, 4H), δ 10.48 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 114.05,115.96, 115.96, 117.27, 117.27, 120.35, 122.59, 122.66, 125.07, 125.07, 125.46, 125.50,126.77, 127.47, 128.26, 129.06, 129.06, 138.24, 138.25, 147.97, 148.18, 148.18, 150.37,152.53, 170.28, 171.21, 173.07. Anal. Calcd for $C_{27}H_{21}FN_8O_2$: C, 59.983; H, 3.914; F, 3.513; N, 20.726; O, 11.862; found: C, 59.997; H, 3.920; F, 3.550; N, 20.701; O, 11.798. m/z 541.64 (M+1).

1-[4-(4-Fluoro-phenylamino)-6-(3-naphthalen-1-l-ureido)-[1,3,5] triazin-3-yl] 3-2-tolyl urea (III_b)

^{1}HNMR (200MHz, DMSO-d_6): 2.56(CH_3, s, 3H), δ7.04-7.20 (Ar-H, m, 7H), δ 7.35 (Ar-H, t, 1H), δ 7.47 (Ar-H, t, 1H), δ 7.56-7.60 (Ar-H, m, 2H), δ 7.68 (Ar-H, t, 1H), δ 7.96-7.98 (Ar-H, m, 3H), δ 10.45 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 17.9, 114.05, 115.96, 115.96, 116.64, 117.27, 117.27, 120.35, 121.32,122.59,122.66, 125.46, 125.46, 125.50, 126.77, 128.26, 129.62, 131.13, 138.25, 147.89, 147.97, 148.18, 150.37, 151.15, 152.53, 171.22, 173.07. Anal. Calcd for $C_{28}H_{23}FN_8O_2$: C, 60.631; H, 4.179; F, 3.425; N, 20.202; O, 11.562; found: C, 60.520; H, 4.111; F, 3.463; N,20.212; O,11.549.m/z 451.67 (M+1).

1-[4-(4-Fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] 3-3-tolyl urea (III_c)

^{1}HNMR (200MHz, DMSO-d_6): δ 2.06 (CH_3, s, 3H), δ 6.78-6.80 (Ar-H, m, 2H), δ 6.97 (Ar-H, t, 1H), δ 7.09-7.23 (Ar-H, m, 5H), δ7.47 (Ar-H, d, 1H), δ 7.56 (Ar-H, t, 1H), δ 7.60 (Ar-H, d, 1H), δ 7.68 (Ar-H, t, 1H), δ 7.96-8.00 (Ar-H, m, 3H), δ 10.46 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 20.7, 114.05, 115.96, 115.96, 17.27, 117.27, 117.97, 120.35, 120.50, 122.59, 122.66, 123.67, 125.46, 125.50, 126.77, 128.02, 128.26, 137.77, 138.25, 144.09, 147.97, 148.18, 148.18, 150.37, 152.53, 170.28, 171.21, 173.07. Anal. Calcd for $C_{28}H_{23}FN_8O_2$: C, 60.635; H, 4.179; F, 3.425; N, 20.202; O, 1.562; found: C, 60.600; H, 4.118; F, 3.422; N, 20.233; O, 11.585. m/z 451.67(M+1).

1-[4-(4-Fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] 3-4-tolyl urea (III_d)

^{1}HNMR (200MHz, DMSO-d_6): δ 2.34 (CH3, s, 3H), δ 7.09 (Ar-H, t, 1H), δ 7.20-7.23 (Ar-H, m, 3H), δ (7.46-7.48 (Ar-H, m, 3H), δ 7.56-7.60 (Ar-H, m, 4H), δ 7.68 (Ar-H, t, 1H), δ 7.96-8.00 (Ar-H, m, 3H), δ 10.48 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 21.05, 114.05, 115.96, 115.96, 117.27, 117.27, 120.35, 122.59, 122.66,125.35, 125.36, 125.46, 125.50, 126.77, 128.26, 130.06, 130.06, 135.73, 138.25, 140.24,147.97, 148.18, 148.18, 150.37,152.53, 170.28, 171.21, 173.07. Anal. Calcd for$C_{28}H_{23}FN_8O_2$: C, 60.635; H, 4.179; F, 3.425; N, 20.202; O, 11.562; found: C, 60.582; H, 4.212; F, 3.400; N, 20.201; O, 11.566. m/z 451.67 (M+1).

1-[4-(4-Fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] 3-(2-nitro-phenyl) urea (III_e)

^{1}HNMR (200MHz, DMSO-d_6): δ 6.83 (Ar-H, t, 1H), δ 7.09 (Ar-H, t, 1H), δ7.20-7.28 (Ar-H, m, 4H), δ7.46 (Ar-H, s, 1H), δ 7.48 (Ar-H, s, 1H),δ 7.56-7.60 (Ar-H, m, 3H), δ7.68 (Ar-H, t, 1H), δ 7.96-7.98 (Ar-H, m, 3H), δ 10.99 (NH,s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 114.05, 115.96, 115.96, 117.13, 117.27, 117.27,119.39, 120.35, 122.59, 122.66, 124.75, 125.46, 125.50, 125.78, 126.77, 128.26, 138.25,143.82, 144.42, 144.66, 147.97, 148.18, 150.37, 152.53, 168.59, 170.28, 173.07. Anal.Calcd for $C_{27}H_{20}FN_9O_4$: C, 55.374; H, 3.442; F, 3.243; N, 21.525; O, 16.413; found: C, 55.205; H, 3.444; F, 3.251; N, 21.601; O, 16.413. m/z 481.63 (M+1).

1-**[4-(4-Fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] 3-(3-nitro-phenyl) urea (III_f)**

^{1}HNMR (200MHz, DMSO-d_6): δ 7.09 (Ar-H, t, 1H), δ 7.20-7.23 (Ar-H, m, 3H), δ 7.35 (Ar-H, t, 1H), δ 7.47-7.50 (Ar-H, m, 2H), δ 7.56 (Ar-H, t, 1H), δ 7.60 (Ar-H, d, 1H), δ 7.66-7.71 (Ar-H, m, 2H), δ 7.87 (Ar-H, d, 1H), δ 7.94-8.00 (Ar-H, m, 3H), δ 10.51 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 112.28, 114.05, 115.96, 115.96, 116.65, 117.27, 117.27, 120.35, 122.59, 122.66, 124.21, 125.46, 125.50, 126.77, 127.86, 128.26, 138.25, 145.66, 145.86, 147.97, 148.18, 148.18, 150.37, 152.53, 170.28, 171.21, 173.07. Anal.Calcd for $C_{27}H_{20}FN_9O_4$: C,

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55.374; H, 3.442; F, 3.243; N, 21.525; O, 16.413; found: C, 55.366; H, 3.452; F, 3.242; N, 21.555; O, 16.413. m/z 481.63 (M+1).

1-[4-(4-Fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] 3-(4-nitro-phenyl) urea (III_g)

^{1}HNMR (200MHz, DMSO-d_6): δ 7.09 (Ar-H, t, 1H), δ 7.20-7.26 (Ar-H, m, 5H), δ 7.47 (Ar-H, d, 1H), δ 7.56 (Ar-H, t, 1H), δ 7.60 (Ar-H, d,1H), δ 7.68 (Ar-H, t, 1H), δ 7.94-8.02 (Ar-H, m, 5H), δ 10.48 (NH, s, 5H). ^{13}CNMR(75MHz, DMSO-d_6): 114.05, 114.21, 114.21, 115.96, 115.96, 117.27, 117.27, 120.35, 122.59, 122.66, 125.46, 125.50, 126.77, 127.01, 127.01, 128.26, 138.25, 140.55, 143.19,147.97, 148.18, 148.18, 150.37, 152.53, 170.28, 171.21, 173.07. Anal. Calcd for $C_{27}H_{20}FN_9O_4$: C, 55.374; H, 3.442; F, 3.243; N, 21.525; O, 16.413; found: C, 55.332; H, 3.444; F, 3.232; N, 21.512; O, 16.413. m/z 481.63 (M+1).

1-(2-Chloro-phenyl)-3-[4-(4-fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] urea (III_h)

^{1}HNMR (200MHz, DMSO-d_6): δ 6.87 (Ar-H, d,1H), δ 7.09 (Ar-H, t, 1H), δ 7.16-7.29 (Ar-H, m, 5H), δ 7.47 (Ar-H, d, 1H), δ 7.56 (Ar-H, t, 1H), δ 7.60 (Ar-H, d, 1H), δ 7.68 (Ar-H, t, 1H), δ 7.95-8.00 (Ar-H, m, 3H), δ 8.59 (Ar-H, d, 1H), δ 10.67 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 114.05, 115.96, 115.96,117.27, 117.27, 119.25, 120.34, 120.35, 122.59, 122.66, 123.95, 125.46, 125.50, 126.77, 128.26, 128.96, 129.89, 138.25, 143.74, 147.97, 148.18, 148.97, 150.37, 152.53, 170.28,170.99, 173.07. Anal. Calcd for $C_{27}H_{20}ClFN_8O_2$: C, 56.390; H, 3.505; Cl, 6.164; F, 3.303; N, 19.484; O, 11.151; found: C, 56.375; H, 3.510; Cl, 6.202; F, 3.322; N, 19.392; O,11.154. m/z 471.08 (M+1).

1-(3-Chloro-phenyl)-3-[4-(4-fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] urea (III_i)

^{1}HNMR (200 MHz, DMSO-d_6): δ 6.86 (Ar-H, d,1H), δ 6.99-7.26 (Ar-H, m, 6H), δ 7.47 (Ar-H, t, 1H), δ 7.56 (Ar-H, t, 1H), δ 7.60 (Ar-H, d, 1H), δ 7.68 (Ar-H, t, 1H), δ 7.95-8.02 (Ar-H, m 4H), δ 10.60 (NH, s, 5H).^{13}CNMR(75MHz, DMSO-d_6): 114.05, 115.96, 115.96, 117.27, 117.27, 120.35, 121.55, 122.59, 122.66, 122.70, 123.55, 125.46, 125.50, 126.77, 128.26, 129.50, 132.60, 138.25, 141, 147.97, 148.18, 148.18, 150.37, 152.53, 170.28, 171.21, 173.07. Anal.Calcd for $C_{27}H_{20}ClFN_8O_2$: C, 56.390; H, 3.505; Cl, 6.164; F, 3.303; N, 19.484; O, 11.151; found: C, 56.402; H, 3.521; Cl, 6.175; F, 2.298; N, 19.500; O, 11.150. m/z 471.08 (M+1).

1-(4-Chloro-phenyl)-3-[4-(4-fluoro-phenylamino)-6-(3-naphthalen-1-yl-ureido)-[1,3,5] triazin-2-yl] urea (III_j)

^{1}HNMR (200MHz, DMSO-d_6): δ 6.91-6.95 (Ar-H, m, 2H), 7.00 (Ar-H, d, 1H), δ7.03 (Ar-H, d, 1H), δ 7.09 (Ar-H, t, 1H), δ 7.16-7.23 (Ar-H, m, 3H), δ 7.47 (Ar-H, d, 1H), δ 7.53-7.72 (Ar-H, m, 3H), δ 7.94-8.01 (Ar-H, m, 3H), δ10.48 (NH, s, 5H). ^{13}CNMR(75 MHz, DMSO-d_6): 114.05, 115.96, 115.96, 117.27, 117.27, 120.35, 122.59, 122.66, 124.49, 124.49, 125.46, 125.50, 126.77, 127.21, 127.21,128.26, 128.81, 138.25, 138.85, 147.97, 148.18, 148.18, 150.37, 152.53, 170.28, 171.27, 173.07.Anal. Calcd for $C_{27}H_{20}ClFN_8O_2$: C, 56.390; H, 3.505; Cl, 6.164; F, 3.303; N, 19.484; O, 11.151; found: C, 56.381; H, 3.501; Cl, 6.152; F, 3.313; N, 19.500; O, 11.132. m/z 471.08 (M+1).

ACKNOWLEDGMENT

The authors are thankful to Mr. Rama rao and Mrs. Latha Reddy, Sai Life Sciences Limited, Hyderabad, India for analysis of ^{1}H NMR, ES Mass samples. We thank Dr. S. Chandrasekhar, Deputy Director, Indian Institute Of Chemical Technology, Hyderabad, India for his support in executing this project and finally Dr. K.Ranga raju, Chairman and Managing director, Sai Life Sciences Limited, Hyderabad, India for his financial support.

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